REMARKS

Reconsideration is respectfully requested. Claims 15-25 stand rejected. Claims 21 and 22 have been canceled. Claims 15-19 and 22-25 have been amended. Support for claim 15 can be found, for example, in the specification and claims as originally filed and on page 3 lines 3-5. Support for amended claims 16-19 can be found, for example, in the specification and claims as originally filed. Support for claim 22-24 can be found for example on page 3 lines 8-16.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Objections to the Claims

Claims 15 has been amended to remove the word "an" as objected to by the Examiner. Applicant respectfully requests withdrawal of this rejection. Note that claim 25 has also been amended to remove the word "an."

Objections to the Specification

The specification has been amended to provide the current status of each application to which the present application claims priority. Applicant respectfully requests withdrawal of this rejection.

Claim Rejection Under 35 U.S.C. § 112, first paragraph

1. Written description

Claims 15-24 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Claim 15 has been amended to recite a "method of treatment of a host with a cellular proliferative disease, comprising contacting said host with amonafide in conjunction with homoharringtonine . . . wherein said cellular proliferative disease is a solid tumor." The "amonafide in conjunction with

homoharringtonine" requirement is adequately supported by the instant specification and therefore complies with the written description requirement. As stated by the Examiner, the

> Applicant has provided sufficient written description for the use of the naphthalimide compound amonafide in conjunction with the antiproliferative agents cisplatin . . . , vinblastine . . . , [and] homoharringtonine for the treatment of fibrosarcoma . . .
> [Page 5, paragraph 3 of the Office Action]

The Examiner argues that the "solid tumor" limitation is not adequately supported by the instant specification. Specifically, the Examiner asserts that

> [G]iven the disparate and distinct nature of all known cancers, there mere exemplification of fibrosarcoma is most certainly not a representative showing of species to then claim the treatment of the entire genus of "solid tumors."
> [Page 8, paragraph 1 of the Office Action]

The Applicant respectfully disagrees. Example 2 in the specification prove that treatment of a solid tumor with amonafide in conjunction with homoharringtonine is effective in slowing the progress of tumor growth.

The RIF-1 fibrosarcoma model was developed in 1980 (Twentyman, P.R. et al., A new mouse tumor model system (RIF-1) for comparison of end-point studies. J. Natl Cancer Inst., 1980 Mar;64(3):595-604). Since that time, it has been used around the world in syngeneic C3H mice as an established solid tumor model for drug screening and experimental cancer therapeutics. For example, a search on http://www.pubmed.gov at the National Library of Medicine and National Institutes of Health website using the search criteria "RIF-1 AND cancer AND C3H" yielded 261 hits. Its chemosensitivities to conventional cancer therapies (antimetabolites, antimitotics, alkylating agents, topoisomerase I and II etc.) are well characterized in the literature and generally correlate with sensitivity to human cell lines in nude mice and with drug sensitivity for human disease. Data from this model has been used to represent efficacy modeling in preclinical studies for FDA filings for drug evaluation in humans. Obviously, the strength of the model is primarily of value for small chemical entities. Many of the established agents today (cisplatin, 5-FU, melphalan, camptothecins, taxanes, etc.) were studied in this model to determine novel treatments and combinations schedules as well as general antineoplastic activity.

One of skill in the art would recognize that this treatment illustrated through the use of the RIF-1 fibrosarcoma model could be similarly applied to other types of solid tumors. The specification provides working examples (Examples 1-2) wherein the modulation of a cellular proliferative disease characterized by a solid tumor is determined. Specifically, the Examples disclose measuring the rate of growth of solid tumors via caliper measurements and using those measurements to determine the tumor volume quadrupling time. Those of skill in the art would be well apprised of additional methods to use in determining success of treatment with the present invention. As such, the "solid tumor" limitation is adequately supported by the instant specification.

2. Enablement

Claims 15-24 stand rejected under 35 U.S.C. §112, first paragraph, allegedly for lack of enablement. Claim 15 has been amended as previously discussed to include the (a) "amonafide in conjunction with homoharringtonine" and (b) "solid tumor" requirements. The (a) requirement is enabled by the instant specification. As stated by the Examiner, the specification is

> enabling for the use of amonafide in conjunction with . . . homoharringtonine . . . for the treatment of fibrosarcoma. [Page 9, paragraph 2 of the Office Action]

The Examiner asserts that

> [In] order to be enabled to practice the present invention, the skilled artisan would have to accept that by administering the presently claimed combination of active agents, all solid tumors known in the art could be treated. . . . Because the specification fails to direct the skilled artisan as to which other tumors aside from fibrosarcoma are known to be sensitive to such a composition, and especially in consideration of the highly complex nature of tumors and cancer in general, the specification, which lacks an objective showing of which solid tumors other than fibrosarcoma could be effectively treated using the claimed combination of active agents, is viewed as lacking an enabling disclosure of the same. [Pages 11-12 of the Office Action]

Applicant respectfully disagrees and respectfully points out that some experimentation, even if complex, is allowable under 35 U.S.C. § 112, first paragraph. MPEP §2164.01 (The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub

nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)). As previously described, the RIF-1 fibrosarcoma model utilized in Example 2 of the instant specification has been used for decades as an established tumor model. Such methods to determine the effect of amonafide in conjunction with homoharringtonine would not require more effort than is normally required in the art. Thus, the specification is enabling for claim 15 and those claims depending therefrom as directed to the treatment of any cellular proliferative disease that is a solid tumor.

Claim Rejection Under 35 U.S.C. § 112, second paragraph

Claims 15-24 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter Applicant regards as the invention. The Examiner asserts that

> [The] very recitation of "naphthalimide comprising" or "antiproliferative agent comprising" fails to clearly delineate whether amonafide and homoharringtonine are required to be present as components of the composition of the naphthalimide and the antiproliferative agent to be administered, or whether such agents are merely an exemplary combination that may be employed in the presently claimed method.
> [Page 18, paragraph 1 of the Office Action]

As previously discussed, claim 15 has been amended to recite a method "comprising contacting said host with amonafide in conjunction with homoharringtonine." Thus, claim 15 is clear and definite.

Claims 15-21 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter Applicant regards as the invention. The Examiner asserts that

> The expression "modulation" is not defined by the claims to properly delineate the effect that is intended from administration of a combination of a naphthalimide and an antiproliferative agent.
> [Page 19 of the Office Action]

Claim 15 has been amended to recite an "amonafide in conjunction with homoharringtonine, each in an amount sufficient to have an anticancer effect on said cellular proliferative disease" requirement. As such, claim 15 is clear and definite.

Therefore, claim 15 and those claims depending therefrom are clear and definite under 35 U.S.C. §112, second paragraph. Applicant respectfully requests that this rejection be withdrawn.

Claim Rejection Under 35 U.S.C. § 103(a)

Claims 15-25 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Scheithauer et al. (*Breast Cancer Research and Therapeutics*, 20:63-67, 1991) (hereinafter "Scheithauer") in view of Jiang et al. (*Investigational New Drugs*, 1:21-25, 1983) (hereinafter "Jiang"). To establish a *prima facie* case of obviousness, there must be some suggestion or motivation in the reference or in the knowledge generally available to one of ordinary skill in the art, to modify the reference and there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicants' disclosure. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

1. Claim 15

As currently amended, method claim 15 recites "contacting said host with amonafide in conjunction with homoharringtonine." On page 20-21 of the Office Action, the Examiner cites Scheithauer as teaching "treatment of patients with advanced breast cancer . . . using amonafide" and Jiang as teaching that "homoharringtonine . . . was known in the art to demonstrate significant antitumor activity in solid tumors, including ovarian, endometrial and breast cancer, as well as sarcoma."

In addition, the Examiner cites the last sentence in Scheithauer, which reads "[amonafide] should therefore be considered for further evaluation and incorporation in combination chemotherapy." The Examiner argues that this provides the motivation to modify Scheithauer:

> One of ordinary skill in the art would have been motivated to use amonafide in conjunction with homoharringtonine for the treatment of breast cancer . . . since each was known separately in the art to have significant therapeutic activity in the treatment of breast tumors. Motivation to administer both compounds flows logically from this shared efficacy and the demonstration in the prior art that each had been previously administered for the same therapeutic endpoint.
> [Page 21-22 of the Office Action]

Applicant respectfully disagrees. Neither reference provides any suggestion or motivation to use amonafide in conjunction with homoharringtonine. M.P.E.P.

§2143.01 I. provides that "obviousness can only be established . . . where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." Neither reference explicitly suggests treatment "with amonafide in conjunction with homoharringtonine" as required by claim 15. The test for an implicit suggestion is provided by the M.P.E.P as well.

> "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab,* 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000).
> [Id.]

The last sentence in Scheithauer cited by the Examiner would not implicitly motivate a person of ordinary skill in the art to reach a treatment "with amonafide in conjunction with homoharringtonine." A myriad of possible agents exist that could be used in conjunction with amonafide. For example, a search of the Food and Drug Administration (FDA) website for pending clinical trials at www.clinicaltrials.gov yielded 659 hits using the key words "breast cancer." As such, no motivation or suggestion exists to select homoharringtonine from hundreds of possible anticancer agents to reach the present invention.

In addition, the Examiner argues that

> [A] common function of each of the compounds would have raised the reasonable expectation of success that the combination of both amonafide and homoharringtonine would have achieved, at a minimum, a potentiated antitumor effect, such that the effect of the agents when combined would have been greater than the effect achieved by either single agent alone . . .
> [Page 22 of the Office Action]

The Applicant respectfully disagrees. As discussed above, there is no motivation provided in either reference to reach a method of treatment "with amonafide in conjunction with homoharringtonine" as required by claim 15. Given the lack of motivation to modify the references, there is no reasonable expectation of success.

Claim 25

In addition, the Examiner asserts that the "composition comprising amonafide and homoharringtonine" of claim 25 is obvious because

> [The] motivation to administer the two compounds in a single formulation would have been *prima facie* obvious to one of ordinary skill in the art,

> since each was known to exhibit efficacy in the treatment of breast cancer and would have been reasonably expected to achieve a greater antitumor effect when combined than when given individually.
> [Page 22 of the Office Action, second paragraph]

However, as discussed above, there is no motivation provided in either reference to reach the method claims of the present invention because of the myriad number of agents that might be given in conjunction with amonafide. Similarly, there is no motivation in either reference to reach a "composition comprising amonafide and homoharringtonine," as required by claim 25. Given the lack of motivation to modify the references, there is no reasonable expectation of success. In addition, Scheithauer's disclosure of "combination chemotherapy" suggests that two agents are administered separately rather than as a physical combination of agents. Unlike Scheithauer, the present invention provides a "composition comprising amonafide and homoharringtonine." Therefore, the references provide no reasonable expectation of success.

The Examiner has failed to establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a). As such, the Applicant respectfully requests the withdrawal of this rejection.

Double Patenting Rejections

Claims 15-24 stand rejected as allegedly unpatentable under the judicially created doctrine of obviousness-type double patenting over the method claims of U.S. Patent No. 6,630,173 (hereinafter the "'173 patent"). As currently amended, claim 15 includes a step of "contacting said host with amonafide in conjunction with homoharringtonine." The method claims of the '173 patent require "contacting said host with a naphthalimide comprising an amonafide and an antiproliferative agent comprising cisplatin." The present invention does not include "an antiproliferative agent comprising cisplatin." As such, the present invention is patentably distinct over the '173 patent.

Claims 15-24 stand provisionally rejected as allegedly unpatentable under the judicially created doctrine of obviousness-type double patenting over the allowed method claims of U.S. Application No. 11/067,074. Method claims 1 and 2 of 11/067,074 require "contacting said host with amonafide in conjunction with an antiproliferative agent" where the agent is selected from a Markush group of antiproliferative agents. Neither of the Markush groups in claims 1 and 2 include homoharringtonine. Thus, the claims of the present invention is patentably distinct over 11/067,074.

Claims 15-24 stand provisionally rejected as allegedly unpatentable under the judicially created doctrine of obviousness-type double patenting over the pending method claims 29-30 and 50-59 of U.S. Application No. 10/976,961. Pending claims 29-30 are directed to a "method of preparing an organic carboxylic acid salt of amonafide." Claims 15-24 of the present invention are directed to methods of treatment. Pending claims 50-59 of 10/976,961 are directed to a "method of treating a subject with cancer comprising the step of administering to the subject an effective amount" of an amonafide analog. Claims 15-24 of the present invention are directed to methods of treatment "with amonafide in conjunction with homoharringtonine." As such, the claims of the present invention are patentably distinct over 10/976,961.

Claims 15-24 stand provisionally rejected as allegedly unpatentable under the judicially created doctrine of obviousness-type double patenting over the pending method claims of U.S. Application No. 10/625,866. The method claims of 10/625,866 are directed to the treatment of an angiogenic disease and require "contacting said host with a cephalotaxine . . . wherein said angiogenic disease is not a solid tumor." Claims 15-24 require the "treatment of a host with a cellular proliferative disease, comprising contacting said host with amonafide in conjunction with homoharringtonine, . . . wherein said cellular proliferative disease is a solid tumor." Thus, the claims of the present invention are patentably extinct over 10/625,866.

Claim 25 stands provisionally rejected as allegedly unpatentable under the judicially created doctrine of obviousness-type double patenting over pending claims 42-44 of U.S. Application No. 10/976,961. Claims 42-44 recite a pharmaceutical composition comprising a naphthalimide analog. Claim 25 of the present invention requires a "pharmaceutical composition comprising amonafide and homoharringtonine." As such, claim 25 is patentably distinct.

Based on the foregoing, Applicant respectfully requests withdrawal of all double patenting rejections.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,
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Dated: June 26, 2006 By: J.P. Bernhardt

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